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(54) IMPROVEMENTS IN OR RELATING TO A MEDICINE FOR THE TREATMENT OF ACNE

(71) I, CHARLES GRUPPER, a French citizen, of 38 rue de Courcelles - 75008 Paris, France, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:

The present invention relates to a medicinal composition for the treatment of acne.

It is known that erythromycin, which was discovered in 1952, has bacteriostatic and bactericidal properties. It is an antibiotic with a very wide anti-bacterial spectrum, but it has no effect on viruses, yeasts and fungi.

The use of this product for the treatment of various diseases of bacterial origin or associated with bacterial symptoms is well known, the product being administered either orally or by injection.

It has also been proposed to apply erythromycin topically in treating skin diseases (pyodermatitis), in a concentration of the order of 1%. The results obtained with such concentrations have proved to be only partially satisfactory and research in that direction has not been pursued.

I have unexpectedly discovered that the admixture of an excipient with erythromycin in a certain concentration of erythromycin higher than previously proposed concentrations provides compositions which are especially efficient with respect to acne, as also are some specific compositions containing erythromycin, at least one other active principle and an excipient. In the latter case, the concentration of erythromycin may be lower than in the absence of such other active principle.

Neither of the abovementioned compositions, i.e. neither (a) that of an excipient with erythromycin nor (b) that of an excipient with erythromycin and at least one other active principle (nor their use in the treatment of acne), appears to have been previously disclosed in the literature. The former compositions (a) contain a concentration of active principle within a specific range and higher than that of known compositions, while the latter compositions (b) contain another specific active principle in addition to erythromycin. Moreover, the use of another specific active principle provides a synergistic or additive as well as the complementary effect sought for in the treatment of acne.

According to one aspect of the invention there is provided a medicinal composition for the treatment of acne and containing erythromycin, preferably in the form of free erythromycin, in a concentration of from 3 to 4.5% inclusive by weight, preferably from 3.8 to 4.5% inclusive by weight, in admixture with a pharmaceutically acceptable excipient.

The medicinal composition may be used in any suitable form for topical administration, especially, for example, in the form of a lotion, gel, cream, unguent or ointment. The lotion from may be aqueous, hydroalcoholic (i.e. a mixture of alcohol and water) or, preferably, alcoholic. The gel, cream, ointment, unguent or like form is preferably constituted by a hydroalcoholic gel.

Still more preferably, the concentration of erythromycin is from about 3.9 to 4.1% by weight, since it has been found that it exhibits its highest effectiveness within that range, i.e.at a concentration of around 4% by weight.

According to another aspect of the invention there is provided another medicinal composition for the treatment of acne and containing a pharmaceutically acceptable excipient, an erythromycin, preferably erythromycin in the free state, in a concentration of from 1.5 to 4.5% inclusive by weight, preferably from 1.9 to 4.5% by weight, and at least

one other active compound consisting of either vitamin A acid or benzoyl peroxide or both in a concentration *c*, expressed in % by weight, defined by the equation:

$$c = x(0.006 \text{ to } 0.1) + (1 - x)(1.5 \text{ to } 25)$$

wherein:

x is a number from 0 to 1;

x (0.006 to 0.1) is the % weight concentration of vitamin A;

(1−x) (1.5 to 25) is the % weight concentration of benzoyl peroxide.

As appears from the above equation, vitamin A acid and benzoyl peroxide can be present simultaneously, in which case x is different from 0 and different from 1; on the other hand, the limit cases are represented by x=0 (presence of only benzoyl peroxide) and by x=1 (presence of only vitamin A). Indeed :

where x is equal to zero, the above equation becomes:

c=1.5 to 25, which means that the concentration of benzoyl peroxide is then between 1.5 and 25% ;

where x is equal to 1, the above equation becomes :

c=0.006 to 0.1, which means that the concentration of vitamin A acid is then between 0.006 and 0.1%.

More limited relative proportion ranges are to be preferred in dependence upon whether the medicine is in the form of a lotion, gel, cream, unguent or ointment.

In the case of an aqueous, hydroalcoholic or, preferably, alcoholic lotion of erythromycin, the medicine preferably contains x(0.025 to 0.1) % of vitamin A acid and (1−x)(1.5 to 25)% of benzoyl peroxide ; if vitamin A acid is present and there is no benzoyl peroxide, the concentration of vitamin A acid is preferably between 0.025 and 0.1 % ; if there is benzoyl peroxide and there is no vitamin A acid, the proportion of benzoyl peroxide is preferably from 1.5 to 25%. All these percent proportions are by weight.

In the case of a medicine in the form of a gel, cream, unguent or ointment, it preferably contains x(0.006 to 0.05) % of vitamin A acid and (1−x)(1.5 to 25) % of benzoyl peroxide, which means that, in the absence of benzoyl peroxide, the proportion of vitamin A acid is preferably from 0.006 to 0.05 % and in the absence of vitamin A acid the proportion of benzoyl peroxide is preferably from 1.5 to 25 %.

As can be seen from the above equations, at equal concentrations and in additive or synergistic admixture with the same proportion of erythromycin, vitamin A acid is much more active than benzoyl peroxide.

The excipient may be selected from all the excipients usually employed in pharmacology, but for an alcoholic lotion, it preferably consists of a mixture of ethyl alcohol and a diol, or a mixture of ethyl alcohol, a diol, e.g. propylene glycol, and an alkyl ether of diol, e.g. monoethyl ether of ethylene glycol.

A medicine embodying the invention may also be effectively used in the topical treatment of complaints where a loss of substances occurs such as ulcers, eschars and burns, in which case it preferably comprises at least 5% by weight of benzoyl peroxide in admixture with erythromycin and possibly also vitamin A acid. Generally, medicines embodying the invention, applied topically, display the following properties :

antimicrobic and antiinflammatory action (due to the presence of erythromycin) ;

maturing action on epidermal structures, normalizing action with respect to keratinization, stimulating effect on wound healing or repair (due to the presence of vitamin A acid) ;

oxygen donor action (due to the presence of benzoyl peroxide) ;

exfoliating or desquamating action (due to the presence of vitamin A acid and of benzoyl peroxide) ;

favourable modifying action on the usual cutaneous flora of acne (inhibiting effect on Propionobacter and antilipase activity reducing the disengagement of saturated or free fatty acids, especially those with 12 carbon atoms, which exhibit acnegenic action), due to the presence of erythromycin and/or vitamin A and/or benzoyl peroxide.

Other characterizing features and advantages of compositions embodying the present invention will appear from the following description, given by way of example only, of such embodiments (Examples 1 to 16) and excipients for incorporation into such embodiments (Examples 17 to 23).

It is recalled that the vitamin A acid compound is obtained by substituting a carboxyl function for the primary alcohol function of vitamin A.

Examples 1 to 3

Alcoholic lotions with 3.8; 4 and 4.5 % by weight of erythromycin, respectively.

Example 4
Hydroalcoholic gels with 3.8 ; 4 and 4.5 % by weight of erythromycin, respectively.

Example 5
Lotion with 4 % by weight of erythromycin and 0.05 % by weight of vitamin A acid.

Example 6
Lotion with 4 % by weight of erythromycin and 0.025 % by weight of vitamin A acid.

Example 7
Lotion with 4 % by weight of erythromycin, 0.025 % by weight of vitamin A acid and 2.5 % of benzoyl peroxide.

Examples 8 to 10
Hydroalcoholic gels with 3, 8 % ; 4 % and 4.5 % by weight of erythromycin, respectively.

Example 11
Hydroalcoholic gel with 4 % by weight of erythromycin and 0.012 % by weight of vitamin A acid.

Example 12
Hydroalcoholic gel with 4 % by weight of erythromycin and 0.025 % by weight of vitamin A acid.

Example 13
Hydroalcoholic gel with 4 % by weight of erythromycin and 2.5 % by weight of benzoyl peroxide.

Example 14
Hydroalcoholic gel with 4 % by weight of erythromycin and 5 % by weight of benzoyl peroxide.

Example 15
Hydroalcoholic gel with 4 % by weight of erythromycin and 22 % by weight of benzoyl peroxide.

Example 16
Hydroalcoholic gel with 4 % by weight of erythromycin, 0.025 % by weight of vitamin A acid and 2.5 % by weight of benzoyl peroxide.

Example 17
Excipient for alcoholic lotion :
- 95° ethyl alcohol 40 cc
- monoethyl ether of ethylene glycol 40 cc
- propylene glycol 20 cc

Example 18
Excipient for alcoholic lotion :
- ethyl alcohol 70 cc
- propylene glycol 30 cc

Example 19
Excipient for alcoholic lotion :
- ethyl alcohol 50 cc
- propylene glycol 50 cc

Example 20
Excipient for gel:
- ethyl alcohol 50 cc
- product known under the commercial denomination "Carbopol* 940" (carboxyvinyl polymer) 0.5 cc
- water 50 cc

* Carbopol is a Registered Trade Mark

Example 21

Excipient for gel :

- ethyl alcohol	75 cc
- product known under the commercial denomination "Carbopol 940" (carboxyvinyl polymer)	0.5 cc
- water	25 cc

Example 22

Excipient for gel :

- colloidal aluminium and magnesium silicate	2.5 g
- hydroxypropylmethyl cellulose (or hydroxypropyl cellulose)	1 g
- polyethylene lauryl ether	6 g
- ethyl alcohol	42 g
- citric acid	0.55 g
- perfume	0.2 g
- purified water	95 g

Example 23

Excipient for gel :

- carboxyvinyl resin	1.5 g
- triethanolamine	1.5 g
- disodium tetracemate (disodium ethylene diamino tetraacetate)	0.05 g
- propylene glycol	5 g
- distilled water, qs	100 cc

The excipients of the lotions or the gels based on benzoyl peroxide also contain an adequate amount of antioxidant selected from these mentioned in the French pharmacopoeia.

Medicines embodying the invention, applied topically, have given the following results in the treatment of acne :

spectacular reduction in the number of comedos as well as inflammatory lesions (doubled effectiveness compared with a 2 % erythromycin solution) ; excellent results are obtained when used as an inflammatory agents and, to a lesser degree, as a microcystic agent in the case of application of the medicine based on erythromycin without any other active principle, or as both an inflammatory and a microcystic agent when erythromycin is in admixture with at least one of the other above-mentioned active principles ;

relapses, if any, yield more rapidly and more completely than in the case of treatment with a 2 % solution. Relapses which occurred after treatment with the 2% solution were not removed by further treatment with the said 2% solution, but were successfully treated by means of a solution or the gel embodying the present invention at a concentration between 3 and 4.5 %;

at equal concentrations, the gel is a little more effective than the lotion ; indeed, it has high penetrating power, so that it quite rapidly disappears from the surface of the skin, contrary to the lotion whose drying effect is not obtained until it evaporates ; such an effect, which is obtained by using the gel, is more specially sought for in the treatment of diffuse seborrhea states of the face or the back. Moreover, the gel treatment is less often followed by relapses or recurrencs than the 4 % lotion treatment, frequently resulting in a reduction of two or even three degrees in the acne classification according to PLEWIG and KLIGMAN, together with longer remissions ;

the synergistic and complementary effect mentioned above is evidenced by the fact that the application of the medicine according to any one of Examples 5 to 7 and 11 to 16 is more efficient than the successive application of two or three medicines each containing an aforementioned proportion of only one of the three active principles mentioned above, namely erythromycin, vitamin A acid and benzoyl peroxide. As a matter of fact, the use of vitamin A acid and/or benzoyl peroxide in proportions within the above-defined general ranges allows the various pathological symptons of the acne disease to be reduced more rapidly and more effectively than in the case of separate and successive use of the three active constituents.

WHAT I CLAIM IS:-

1. A medicinal composition containing erythromycin in a concentration of from 3 to 4.5 % inclusive by weight, in admixture with a pharmaceutically acceptable excipient.

2. A medicinal composition according to claim 1, wherein the erythromycin is in the

form of free erythromycin.

3. A medicinal composition according to claim 1 or claim 2, wherein the concentration of the erythromycin is from 3.8 to 4.5 % inclusive by weight.

4. A medicinal composition according to claim 3, wherein the concentration of erythromycin is from 3.9 to 4.1 % inclusive by weight.

5. A medicinal composition according to any one of the preceding claims, which is in the form of an aqueous, hydroalcoholic or alcoholic lotion.

6. A medicinal composition according to claim 5, which is in the form of an alcoholic lotion.

7. A medicinal composition according to any one of claims 1 to 4, which is in the form of a gel, cream, unguent or ointment.

8. A medicinal composition according to claim 7, which is in the form of a hydroalcoholic gel.

9. A medicinal composition containing an erythromycin, in a concentration of from 1.5 to 4.5 % inclusive by weight, in admixture with a pharmaceutically acceptable excipient, and at least one other active component consisting of vitamin A acid, or benzoyl peroxide, or both, in a concentration *c*, expressed in percent by weight, defined by the equation:

$$c = x(0.006 \text{ to } 0.1) + (1-x)(1.5 \text{ to } 25)$$

wherein

x is a number from 0 to 1

x(0.006 to 0.1) is the % concentration by weight of vitamin A acid

(1−x)(1.5 to 25) is the % concentration by weight of benzoyl peroxide.

10. A medicinal composition according to claim 9, wherein the erythromycin is in the form of free erythromycin.

11. A medicinal composition according to claim 9 or claim 10 wherein the concentration of the erythromycin is from 1.9 to 4.5 % inclusive by weight.

12. A medicinal composition according to claim 9, claim 10, or claim 11 which is in the form of an aqueous, hydroalcoholic or alcoholic lotion of the said erythromycin, containing x(0.025 to 0.1) % by weight of vitamin A acid and (1−x)(1.5 to 25) % by weight of benzoyl peroxide.

13. A medicinal composition according to claim 12, which is in the form of an alcoholic lotion.

14. A medicinal composition according to claim 9, claim 10 or claim 11, which is in the form of a gel, cream, unguent or ointment, containing x(0.006 to 0.05) % by weight of a vitamin A acid and (1−x)(1.5 to 25) % by weight of benzoyl peroxide.

15. A medicinal composition according to any one of claims 5 to 14, which contains from 5 to 25 % inclusive by weight of benzoyl peroxide.

16. A medicinal composition according to claim 5 or claim 13, wherein the excipient consists of a mixture of ethyl alcohol and a diol.

17. A medicinal composition according to claim 15, wherein the diol is propylene glycol.

18. A medicinal composition according to claim 5 or claim 13, wherein the excipient consists of a mixture of ethyl alcohol, a diol, and an alkyl ether of a diol.

19. A medicinal composition according to claim 18, wherein the diol is propylene glycol.

20. A medicinal composition according to claim 18 or claim 19, wherein the alkyl ether of a diol is the monoethyl ether or ethylene glycol.

21. A medicinal composition according to claim 14, wherein the excipient is a hydroalcoholic gel.

22. A medicinal composition according to any one of the preceding claims substantially as described and exemplified.

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Abstract

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